

# Leptomeningeal Carcinomatosis of Prostate Cancer: A Case Report and Review of the Literature

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Leptomeningeal carcinomatosis is a rare complication of prostate cancer. It is likely underdiagnosed as suggested by autopsy studies and is expected to become more prevalent with increasing survival of prostate cancer patients. Prostate cancer leptomeningeal carcinomatosis is associated with rapid functional decline and a median survival of approximately 1 month. Diagnosis is challenging because the clinical manifestations are varied, and no gold-standard diagnostic approach exists. Treatment of prostate cancer leptomeningeal carcinomatosis is not standardized and multiple approaches have been reported, mostly as case studies. Herein we report a case of a 73-year-old patient with metastatic castration-resistant prostate cancer who presented to our clinic with subacute cognitive decline, ataxia, and urinary incontinence, and was found to have leptomeningeal carcinomatosis.

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## KEY WORDS

Prostate cancer • Leptomeningeal carcinomatosis • Central nervous system metastasis

**A** 73-year-old man with a history of metastatic castration-resistant prostate cancer (mCRPC) presented for follow-up in clinic. The patient was first diagnosed with de novo metastatic prostate cancer 26 months prior, with an initial prostate-specific antigen (PSA) level of 453 ng/mL, biopsy Gleason score of 5+5, extensive bony disease, as well

as retroperitoneal and ileac chain lymphadenopathy. The patient was initially treated with bicalutamide and leuprolide with a good biochemical response and symptomatic improvement; however, he ultimately progressed through several therapies, including 6 cycles of docetaxel, and most recently, abiraterone plus prednisone. The patient's family had noticed

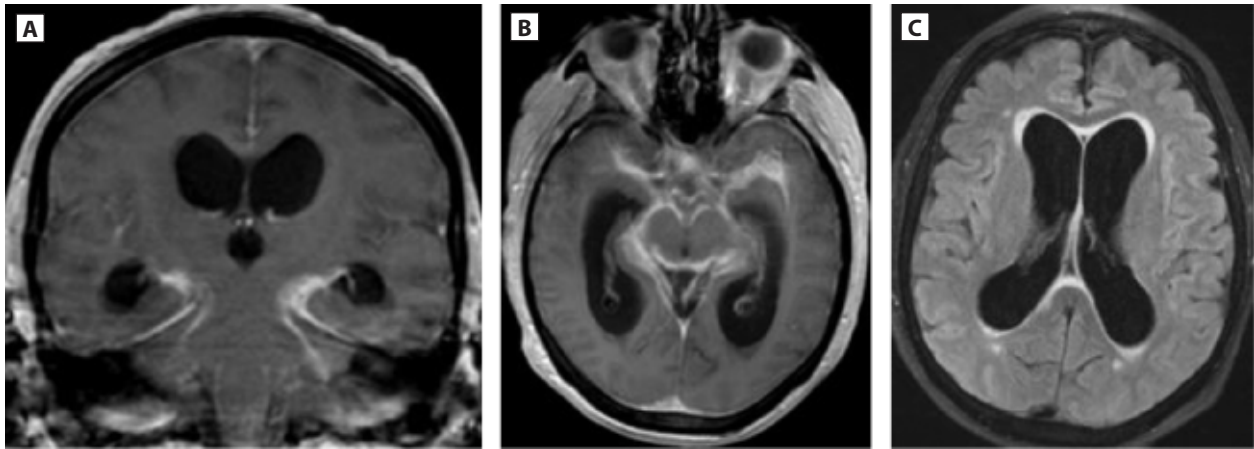


Figure 1. Brain MRI images of our patient with prostate cancer leptomeningeal carcinomatosis. (A) Post-contrast T1 coronal imaging demonstrates enhancement of leptomeninges in the basal cistern and dilatation of the lateral ventricles. (B) Post-contrast T1 axial imaging demonstrates enhancement of the leptomeninges in the bilateral Sylvian fissures and surface of the brainstem. (C) Axial FLAIR imaging demonstrates rounded margin of the dilated lateral ventricles with high FLAIR signal rim at the periventricular ependymal surface, suggesting active hydrocephalus.

that over 2 months the patient had become gradually more fatigued, despite increasing his prednisone dose. Additionally, in recent weeks he manifested lethargy, confusion, urinary incontinence, and difficulty ambulating with multiple falls.

On physical examination, the patient was alert and oriented to person only, able to answer yes/no questions, and could only partially follow simple commands. His cranial nerve examination was intact, as were his strength, sensation, and reflexes throughout his extremities.

Most recent laboratory results had shown interval increase of his PSA from a nadir of 18 to 93 ng/mL. Other results, including a complete blood count and metabolic panel, did not show any significant alterations from recent baseline, except for a serum sodium level of 128 mEq/L. As the patient's symptoms had progressed rapidly and as his presentation was concerning for a possibly unrelated reversible condition, the patient was hospitalized for further workup. Importantly, restaging CT of the chest, abdomen, and pelvis demonstrated stable disease. CT of the head showed ventriculomegaly concerning for mild hydrocephalus versus normal pressure hydrocephalus. MRI with

contrast of his brain showed communicating hydrocephalus with transependymal edema secondary to diffuse, thick leptomeningeal spread of his malignancy (Figure 1). A lumbar puncture was considered to confirm the diagnosis and to rule out infection; however, after discussion with the patient's family, it was agreed that given the patient's overall poor prognosis, this invasive procedure would not be in line with his goals of care, and the patient was discharged to hospice.

## Leptomeningeal Carcinomatosis of Prostate Cancer

### *Epidemiology*

Metastasis to the central nervous system (CNS), and to a greater extent, leptomeningeal carcinomatosis, are exceedingly rare complications of prostate cancer. A study from the MD Anderson Cancer Center examined the records of 7994 patients with prostate cancer between the years 1980 and 1997 and found that 0.7% of them had brain metastasis, but only 1 patient (0.012%) had leptomeningeal spread.<sup>1</sup> A more recent and larger retrospective study from the MD

Anderson Cancer Center has found that between 1979 and 2011, out of 41,830 patients with prostate cancer, only 7 (0.016%) had leptomeningeal metastases.<sup>2</sup> A study conducted in nine Italian hospitals between 2002 and 2010 reported that 3.3% of patients with CRPC had brain metastases, but only 0.96% had leptomeningeal carcinomatosis.<sup>3</sup> Interestingly, older autopsy-series publications described a somewhat higher prevalence of CNS involvement in prostate cancer. One such study examined autopsies of 126 patients with prostate cancer between 1954 and 1981, and found that 14 (11.1%) had metastases to the CNS, of which 12 (9.5%) had some involvement of the dura, but there was no specific data on leptomeningeal carcinomatosis.<sup>4</sup> A similar autopsy series of 91 patients with prostate cancer between 1959 and 1971 found that 4.4% had intracerebral metastasis; however, it was unclear how many had leptomeningeal spread.<sup>5</sup> The higher prevalence of CNS involvement, and specifically, dural involvement, reported in autopsy studies may suggest that most patients with CNS metastases remain undiagnosed. Remarkably, in both autopsy studies described above, it was noted that for most

of these patients, CNS involvement was unknown ante-mortem, and only incidentally found post-mortem. Additionally, some researchers have suggested that the incidence of CNS involvement may be rising in prostate cancer patients due to new therapies and prolonged survival.<sup>6</sup> For example, it has been suggested that the discrepancy between the systemic effectiveness of docetaxel and its very low CNS penetration may also contribute to the potential rise in prostate cancer leptomeningeal carcinomatosis.<sup>3</sup>

### ***Pathophysiology and Natural History of Metastatic Spread of Prostate Cancer to the CNS***

Several mechanisms have been proposed to explain the spread of prostate cancer to the CNS, and specifically to the meninges. In general, leptomeningeal carcinomatosis from solid tumors is most commonly caused by cancers of the breast, lung, gastrointestinal tract, and melanoma.<sup>6</sup> In a retrospective review of 122 patients with intradural metastases of various types of solid cancers diagnosed at Memorial Sloan Kettering Cancer Center between 1999 and 2006, direct extension through skull metastases was deemed the cause of dural involvement in 61% of patients, and 33% of patients were thought to have had hematogenous spread.<sup>7</sup> More specifically addressing prostate cancer, a cadaver study published in 1940 by Batson<sup>8</sup> suggested that tumor cells can invade the CNS from vertebral body metastases through the paravertebral venous plexus. Additionally, as the meningeal tissues are highly vascularized and well oxygenated, hematogenous spread was also suggested as one of the common mechanisms.<sup>9</sup> Finally, as prostate cancer can sometimes metastasize to the skull, direct extension through the dura has likewise been suggested.<sup>10</sup>

However, it had also been proposed that the dura can act as a barrier to prevent such direct invasion, which may explain how only a small minority of patients with metastatic prostate cancer to the skull develop CNS disease.<sup>11</sup>

The CNS is typically not the first site for prostate cancer metastasis. In a study of 31 patients with metastatic prostate cancer to the CNS, all patients had prior metastatic foci to other organs.<sup>3</sup> Compared with a mean duration of 19 months from diagnosis of prostate cancer to appearance of bone metastasis, and 35 months for lung metastasis, one study had shown that CNS spread appears on average 60 months following diagnosis.<sup>12</sup> Other studies have shown shorter mean durations to CNS disease, including averages of 39.1 months,<sup>2</sup> and 43.5 months<sup>3</sup> following diagnosis of prostate cancer. Several studies have suggested that patients with CNS prostate cancer metastasis tend to be significantly younger than patients without CNS involvement.<sup>5,13</sup> The histological type of prostate cancer can also affect the risk for CNS spread. In a retrospective study of 38 patients with ante-mortem intracerebral metastasis, 63% had adenocarcinoma, 26% had small-cell carcinoma, and 11% had transitional-cell carcinoma of the prostate. As the latter are less common forms of prostate cancer, it was concluded that transitional-cell and small-cell prostate carcinomas may be more likely to cause brain metastasis compared with adenocarcinomas.<sup>1</sup>

### ***Clinical Presentation of Prostate Cancer Leptomeningeal Carcinomatosis***

The presentation of leptomeningeal carcinomatosis in prostate cancer can be varied. One study reported the most common reported symptoms to be headaches in 35% of the

patients, confusion (10%), coma (10%), and hyposthenia (10%).<sup>3</sup> Another study reported gait abnormalities as the most common symptoms in 46% of patients, headaches in 38%, weakness in 25%, non-headache pain in 25%, and nausea in 12% of cases. The same study noted that asymmetric weakness is the most common physical examination finding, seen in up to 80% of patients, followed by mental status alterations (50%), cranial nerve palsies (50%, most commonly CN III, IV, VI, VII, and VIII), and seizures in 15% of prostate cancer patients with CNS involvement.<sup>14</sup> Nuchal rigidity was found only in 15% of patients in a different study.<sup>2</sup> Notably, in all prostate cancer patients, with or without CNS involvement, paraneoplastic syndromes, which include neurological symptoms such as neuropathies, cerebellar ataxia, and limbic and brainstem encephalitides, may also occur.<sup>15</sup>

### ***Diagnosis of Prostate Cancer Leptomeningeal Carcinomatosis***

The diagnostic method of leptomeningeal carcinomatosis in prostate cancer has evolved over the years. Currently, MRI with contrast is considered the most sensitive modality, with almost 100% sensitivity. CT scans have a significantly reduced sensitivity of only 26% to 56%.<sup>14</sup> Some researchers have suggested that lumbar puncture (LP) and cerebrospinal fluid (CSF) cytology studies can confirm the diagnosis. Repeating LPs can improve the relatively low sensitivity of CSF cytology, from 50% after a single LP to 90% after three LPs. False-negative CSF cytology results are hence common, and had been attributed to obstruction in CSF flow, insufficient CSF collection, and inadequate handling of samples.<sup>10</sup> One study had shown

that other than abnormal cytology, CSF studies may reveal abnormal protein in 81% of cases, more than 5 cells/ $\mu$ L in 57%, increased opening pressure in 50%, and low glucose in 31% of patients. In 3% of cases, all CSF studies were completely normal.<sup>14</sup> Measuring CSF PSA has also been suggested, as its levels in prostate cancer patients without CNS disease range between 0.2 to 1.4 ng/mL, and between 26.7 to 678 ng/mL in patients with established leptomeningeal carcinomatosis.<sup>11</sup>

### ***Prognosis of Patients With Prostate Cancer Leptomeningeal Carcinomatosis***

In general, patients with prostate cancer leptomeningeal carcinomatosis have poor survival following diagnosis of this complication. In one retrospective study from Italy, only 1 out of 9 patients with this condition survived more than a year, and the median survival was 1 month.<sup>3</sup> A literature review of 14 case studies noted that 12 of these patients survived 1 month or less following diagnosis, 1 patient survived 5 months, and 1 patient survived more than 16 months.<sup>12</sup> An MD Anderson study, which included 7 patients with prostate cancer leptomeningeal

carcinomatosis, had shown a longer median survival of about 15 weeks, with only 1 out of the 7 patients surviving more than 25 weeks.<sup>2</sup> Of note, some factors, such as preserved cognition, controlled systemic disease, normal CSF glucose, and low CSF protein, were associated with improved survival.<sup>2</sup>

### ***Treatment and Palliation for Patients With Prostate Cancer Leptomeningeal Carcinomatosis***

There is currently no standard of care in the treatment of prostate cancer leptomeningeal carcinomatosis, and treatment options are largely based on expert opinion and local practices. One retrospective study of prostate and other genitourinary cancer patients with leptomeningeal carcinomatosis from the MD Anderson Cancer Center identified 31 patients with this condition. Of these 31 patients, 11 received both intrathecal chemotherapy (methotrexate, cytarabine, or topotecan) and radiation therapy, 5 patients received only intrathecal chemotherapy, 7 patients received only radiation therapy, and 8 patients did not receive either. No significant difference in survival was observed between the

groups.<sup>2</sup> Other proposed treatment modalities include hormonal treatment (in castration-sensitive prostate cancer), corticosteroids, and debulking surgery. However, all these treatments have been associated with poor outcomes, and survival was measured in weeks for most patients.<sup>11,12</sup> Because patients with prostate cancer leptomeningeal carcinomatosis tend to have a very limited survival and poor prognosis in general, and as this complication is associated with highly burdensome symptoms, some researchers have suggested that the treatment approach should include a palliative care referral as soon as the diagnosis is made.<sup>2</sup>

## **Conclusions**

Leptomeningeal carcinomatosis is an exceedingly rare complication of prostate cancer; however, its incidence may increase as prostate cancer patients survive longer with new therapies. Its presentation is varied and nonspecific, with most patients having either headaches or gait abnormalities, as well as an abnormal neurological examination. MRI is considered the most sensitive diagnostic approach and is gradually taking the place of CSF studies

## **MAIN POINTS**

- Leptomeningeal carcinomatosis is an exceedingly rare complication of prostate cancer; however, its incidence may increase as prostate cancer patients survive longer with new therapies.
- Its presentation is varied and nonspecific, with most patients having either headaches or gait abnormalities, as well as an abnormal neurological examination.
- MRI is considered the most sensitive diagnostic approach and is gradually taking the place of CSF studies as the gold standard for diagnosis.
- Once diagnosed, patients with prostate cancer leptomeningeal carcinomatosis have a poor prognosis, with survival of less than 1 month in most cases.
- Several treatments, including radiation therapy, intrathecal chemotherapy, steroids, and debulking surgery have been suggested, but none have shown a significant improvement in survival.

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